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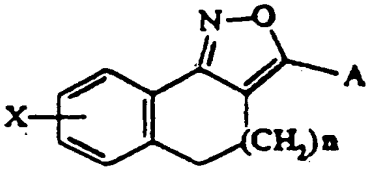
(57) Abstract

4,5-Dihydronaphth[1,2-c]isoxazole derivatives of general formula (I), where A, X and n are defined herein are disclosed. Such compounds are useful as serotonin 5-HT_3 antagonists. These compounds are useful for the treatment of anxiety, psychiatric disorders, nausea, vomiting and drug dependency.



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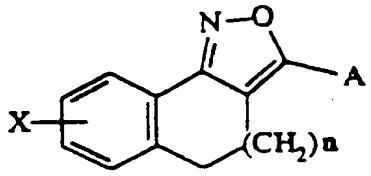
4,5-DIHYDRONAPHTH[1,2-C]ISOXAZOLES AND DERIVATIVES THEREOF HAVING CNS ACTIVITY

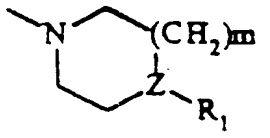
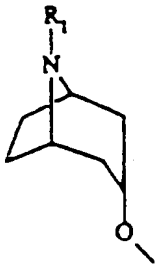
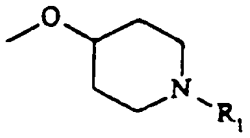
The present invention is directed to certain novel compounds and their use as pharmaceutical agents having unique central nervous system activity.

This invention relates to 4,5-dihydronaphth[1,2-c]isoxazoles and derivatives thereof, and their use as serotonin 5-HT, antagonists, which may be useful for the treatment of anxiety, psychiatric disorders, schizophrenia, nausea, vomiting and the control of drug dependency, of general formula (I):



(I)

wherein A is hydrogen, hydroxy,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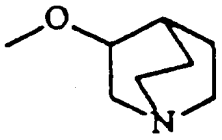


wherein

R_1 is hydrogen, an alkyl group of 1 to 6 carbons, optionally substituted with hydroxy, alkoxy or amino substitution; aryl or heteroaryl, optionally substituted with halogen, hydroxy or alkoxy; or benzyl optionally substituted with halogen, hydroxy or alkoxy;

n is an integer of 1 or 2;

Z is nitrogen, CH or C(OH);

m is an integer of 1 to 3; and

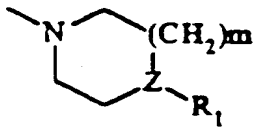
X is hydrogen, hydroxy or alkoxy;

or a pharmaceutically acceptable additional salt thereof, or where applicable, a geometric or optical isomer or racemic mixture thereof.

The present invention also relates to a process for preparing these compounds, pharmaceutically acceptable addition salts thereof, as well as the pharmaceutical acceptable compositions thereof, and a method of using the compounds as seroton 5-HT, antagonists.

Throughout the specification and appended claims, a given chemical formula or name shall encompass all stereo and optical isomers where such isomers exist. Additionally, a given chemical formula or name shall encompass the pharmaceutically acceptable additional salts thereof.

In a preferred embodiment of the invention are compounds of formula (I) wherein

A is 

wherein

R_1 is hydrogen, an alkyl group of 1 to 6 carbons, optionally substituted with hydroxy, alkoxy or amino substitution; aryl or heteroaryl, optionally substituted with halogen, hydroxy or alkoxy; or benzyl optionally substituted with halogen, hydroxy or alkoxy;

n is an integer of 1 or 2;

Z is nitrogen;

m is an integer of 1 to 3; and

X is hydrogen, hydroxy or alkoxy.

More preferred, are compounds of formula (I) wherein

R_1 is hydrogen, or an alkyl group of 1 to 3 carbons;

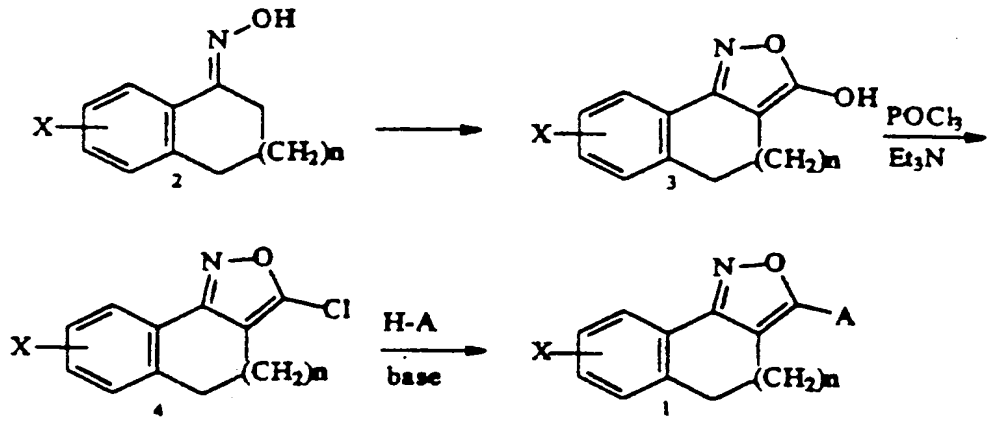
n is 1;

Z is nitrogen;

m is 1 or 2; and

X is hydrogen.

The novel compounds of the present invention and the intermediates thereto may be prepared by the reaction sequence illustrated hereinbelow. The substituents Z, m, n and X are generally as defined above unless otherwise indicated.



According to the preparation scheme, hydroxyisoxazoles 3 are prepared from oximes 2 in a solvent such as tetrahydrofuran (THF) at a temperature of from about 25°C to about reflux temperature of the solvent for a period of from about 0.25 to about 4 hours according to the methods of Griffiths and Olofson (Jerome S. Griffiths, *et al.*, J. Chem. Soc. C, 974 (1971) and G.N. Barber and R.A. Olofson, J. Org. Chem. 43, 3015 (1978)). The hydroxyisoxazoles 3 are converted to chloroisoxazoles 4 via

treatment with phosphorous oxychloride in the presence of a suitable base, such as triethylamine, at a temperature of from about 100° to about 200°C for a period of from about 0.25 to about 4 hours in a manner similar to that utilized by Adembri *et al.* (G. Adembri and P.Tedeschi, **Bull. Sci. Fac. Chim. Ind. Bologna 23**, 203 (1965)). Intermediates **4** are treated with an appropriate nucleophile H-A (wherein A is defined hereinbefore) at a temperature of from about 100° to about 200° C with or without added base in an appropriate solvent, such as N-methylpyrrolidinone, to provide the novel compounds **1** of the invention.

These compounds may be prepared by the following representative examples. The examples are exemplary and should not be construed as limiting the invention disclosed herein.

EXAMPLE 1

3-Chloro-4,5-dihydronaphth[1,2-c]isoxazole

To a stirred mixture of 4,5-dihydronaphth[1,2-c]isoxazol-3-(3aH)-one (7.25g, 38.77mmol) in phosphorus oxychloride (10.84ml, 116.3mmol), triethylamine (5.40ml, 38.77mmol) was added

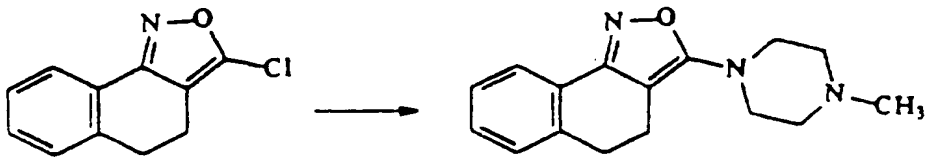
dropwise. After completion of addition, the mixture was heated to reflux while stirring. After 2 hours, no starting material remained as shown by TLC [silica, ethylacetate (EtOAc)]. The mixture was cooled to room temperature, poured into 300 ml of ice water, and extracted with CH_2Cl_2. The organic extracts were combined, dried over $MgSO_4$ and concentrated *in vacuo*. The resultant solid was filtered through silica using CH_2Cl_2 eluent to provide 6.2g of crude product. This crude product was recrystallized from a minimum of heptane to provide a product as needles, mp of 57-59°C, homogeneous by thin layer chromatography (TLC) [silica, CH_2Cl_2, R_f=0.80]. The Infrared (IR) ($CHCl_3$), nuclear magnetic resonance (NMR) ($CDCl_3$), and Mass Spectrum (M^+=205, EI, 70eV) were consistent with the structure. The yield was 5.417g (26.4mmol, 68.16%).

Elemental Analysis

	Calculated	Found
C	64.25	64.02
H	3.92	3.86
Cl	17.24	
N	6.81	6.77
O	7.78	

EXAMPLE 2

3-(4-Methyl-1-piperazinyl)-4,5-dihydronaphth[1,2-c]isoxazole



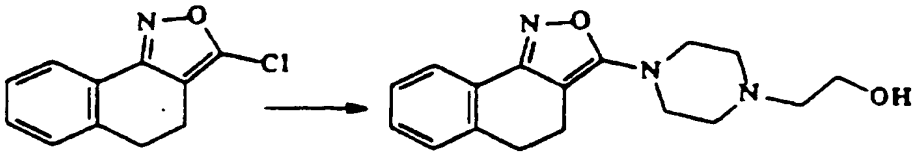
A stirred mixture of 3-chloro-4,5-dihydronaphth[1,2-c]isoxazole (2.65g, 12.93mmol), N-methyl piperazine (30ml, 270.4mmol) and K_2CO_3 (3.57g, 25.87mmol) under N_2 was lowered into an oil bath preheated to 150°C. The mixture was heated while stirring under N_2 for 2 hours. At that time, TLC [CH_2Cl_2] showed no remaining starting material. The mixture was removed from the heating bath and allowed to cool to room temperature. It was then partitioned between heptane/H_2O. The heptane phase was washed with water, dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield a solid. This crude product was recrystallized from heptane/ether (Et_2O) to provide the product as needles, mp of 92-94°C, homogeneous by TLC [silica, 1:1 CH_3OH:EtOAc, R_f=0.39]. The IR ($CHCl_3$), NMR ($CDCl_3$) and Mass Spectrum (M^+=269, EI, 70eV) were consistent with the structure. The yield was 1.2555g (4.67mmol, 36.09%).

Elemental Analysis

	Calculated	Found
C	71.35	71.34
H	7.11	6.98
N	15.60	15.78
O	5.94	

EXAMPLE 3

3-(4-(2-Hydroxyethyl)-1-piperazinyl)-4,5-dihydronaphth[1,2-c]isoxazole



A stirred mixture of 3-chloro-4,5-dihydronaphth[1,2-c]isoxazole (3.0g, 14.63mmol), 1-(2-hydroxyethyl)-piperazine (17.95ml, 146.3mmol) and K_2O_3 (4.1g, 29.3mmol) in 18ml of N-methlypyrrolidinone under N_2 was lowered into an oil bath preheated to 150°C. The mixture was heated while stirring under N_2 for 1 hour. At that time, TLC (CH_2Cl_2) showed no remaining starting material. The mixture was removed from the heating bath, allowed to cool to room temperature, and diluted with H_2O. Upon the addition of heptane, a solid precipitated. The solid was collected, washed with heptane and H_2O, and dried *in vacuo*

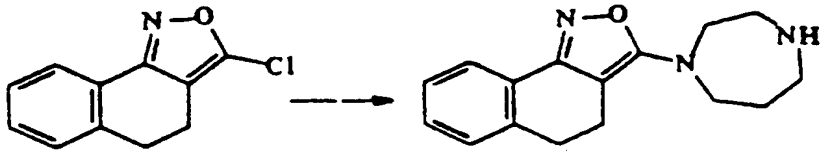
(0.1mm) at 85°C overnight to provide pure product, mp of 137-138°C, homogeneous by TLC [silica, 1:1 CH_3OH:EtOAc, Rf=0.67]. The IR ($CHCl_3$), NMR ($CDCl_3$) and Mass Spectrum (M⁺=299, EI, 70eV) were consistent with the structure. The yield was 2.603g (8.70mmol, 59.47%).

Elemental Analysis

	Calculated	Found
C	68.21	68.12
H	7.07	7.01
N	14.04	14.14
O	10.69	

EXAMPLE 4

3-(1-Homopiperazinyl)-4,5-dihydronaphth[1,2-c]isoxazole



A stirred mixture of 3-chloro-4,5-dihydronaphth[1,2-c]isoxazole (3.0g, 14.63 mmol) homopiperazine (14.66g, 146.3 mmol) and K_2CO_3 (4.04g, 29.3mmol) in 16ml of N-methyl-pyrrolidinone under N_2 was lowered into an oil bath preheated to 150°C. The mixture was heated while stirring under N_2 for 45 minutes. At that time, TLC (CH_2Cl_2) showed no remaining

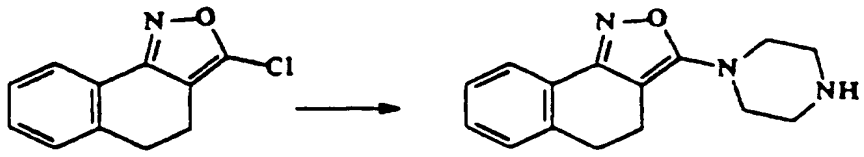
starting material. The mixture was removed from the heating bath, allowed to cool to room temperature, diluted with H_2O and extracted with Et_2O. The Et_2O phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude solid obtained was recrystallized from heptane/Et_2O and dried *in vacuo* (0.1mm) at 85°C overnight to provide pure product, mp of 79-81°C, homogeneous by TLC [silica, 1:1 CH_3OH:EtOAc, Rf=0.17]. The IR ($CHCl_3$), NMR ($CDCl_3$) and Mass Spectrum (M^+=269, EI, 70eV) were consistent with the structure. The yield was 1.969g (7.32mmol, 50.03%).

Elemental Analysis

	Calculated	Found
C	71.35	71.45
H	7.11	7.29
N	15.60	15.56
O	5.94	

EXAMPLE 5

3-(1-Piperazinyl)-4,5-dihydronaphth[1,2-c]isoxazole



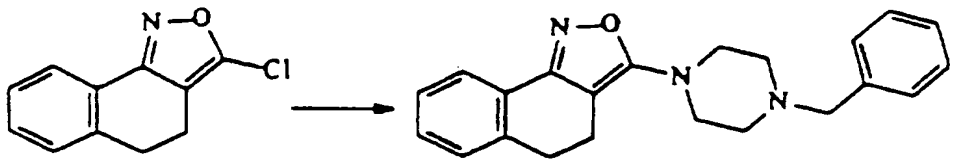
A stirred mixture of 3-chloro-4,5-dihydronaphth[1,2-c]isoxazole (5.0g, 24.4mmol), piperazine (34.2g, 397.7mmol) and K_2CO_3 (6.73g, 48.7mmol) in 40ml of N-methylpyrrolidinone under N_2 was lowered into an oil bath preheated to 150°C. The mixture was heated while stirring under N_2 for 45 minutes. At that time, TLC (CH_2Cl_2) showed no remaining starting material. The mixture was removed from the heating bath, allowed to cool to room temperature and extracted with Et_2O. This organic phase was washed twice with H_2O, dried over $MgSO_4$, filtered and concentrated *in vacuo* to obtain a crude solid. The solid was collected, recrystallized from heptane/Et_2O and dried *in vacuo* (0.1mm) at 85°C to provide pure product, mp of 97-99°C, homogeneous by TLC [silica, 1:1 CH_3OH:CH_2Cl_2, Rf=0.35]. The IR ($CHCl_3$), NMR ($CDCl_3$) and Mass Spectrum (M^+=255, EI, 70eV) were consistent with the structure. The yield was 3.372g (13.22mmol, 54.19%).

Elemental Analysis

	Calculated	Found
C	70.56	70.38
H	6.71	6.67
N	16.46	16.47
O	6.27	

EXAMPLE 6

3-(4-Benzyl-1-piperazinyl)4,5-dihydronaphth[1,2-c]isoxazole



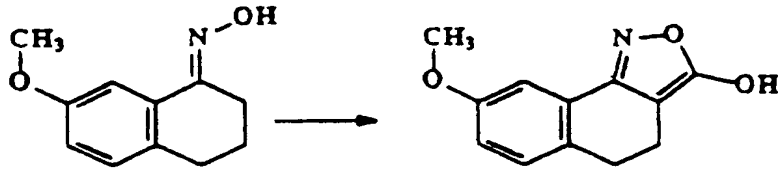
A stirred mixture of 3-chloro-4,5-dihydronaphth[1,2-c]isoxazole (2.0g, 9.75mmol), 1-benzylpiperazine (17ml, 97.5mmol) and K_2CO_3 (2.7g, 19.5mmol) in 18ml of N-methylpyrrolidinone under N_2 was lowered into an oil bath preheated to 150°C. The mixture was heated while stirring under N_2 for 2 hours. At that time, TLC (CH_2Cl_2) showed no remaining starting material. The mixture was removed from the heating bath, allowed to cool to room temperature and extracted with heptane. The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo* to obtain a crude solid. The solid was collected, titrated with Et_2O, recrystallized from Et_2O and dried *in vacuo* (0.1mm) at 85°C to provide pure product, mp of 164-166°C, homogeneous by TLC [silica, 1:1 EtOAc, Rf=0.80]. The IR ($CHCl_3$), NMR ($CDCl_3$) and Mass Spectrum (M^+=345, EI, 70eV) were consistent with the structure. The yield was 1.219g (3.53mmol, 36.24%).

Elemental Analysis

	Calculated	Found
C	76.49	76.49
H	6.71	6.85
N	12.16	12.09
O	4.63	

EXAMPLE 7

3-Hydroxy-8-methoxy-4,5-dihydronaphth[1,2-c]isoxazole



To a mechanically stirred mixture of 7-methoxy α-tetralone oxime (5.0g, 26.18mmol) in anhydrous THF (150ml) at 0°C under N_2 was slowly added n-butyl-lithium (n-BuLi) (23.0ml of a 2.5M solution in hexane, 57.60mmol). The mixture was stirred at 0°C for 30 minutes, then CO_2 gas was bubbled into the solution. (As this addition progressed, a solid precipitate began to form). After 15 minutes, CO_2 addition was stopped and N_2 flow was restored. The thick mixture was stirred and warmed slowly to room temperature for 1¼ hours, then 6N H_2SO_4 (150ml) was slowly added which dissolved the solids. The TLC showed traces of starting oxime and a mixture of desired product and an

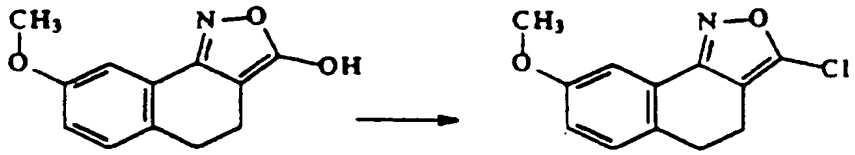
intermediate which was not isolated. Stirring was continued for 4 hours at which time the intermediate was completely converted to product. The mixture was extracted exhaustively with EtOAc. The organic fractions were combined, washed once with H_2O, once with brine, dried over $MgSO_4$ and filtered. Concentration *in vacuo* caused the precipitation of a solid which was collected, titrated with EtOAc, and dried *in vacuo* to provide the product as a solid, mp of 135-138°C, homogeneous by TLC [silica, 10:90 CH_3OH:EtOAc, Rf=0.46]. The IR (KBr), NMR (DMSO-d_6) and Mass Spectrum (M^+=217, EI, 70eV) were consistent with the structure. The yield was 2.0496g (9.45mmol, 36.08%).

Elemental Analysis

	Calculated	Found
C	66.35	66.02
H	5.10	5.03
N	6.45	6.22
O	22.10	

EXAMPLE 8

3-Chloro-8-methoxy-4,5-dihydronaphth[1,2-c]isoxazole



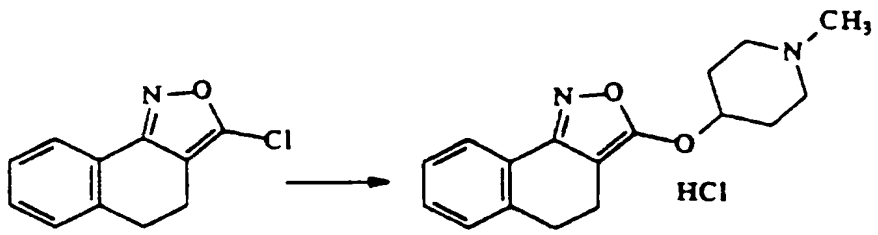
To a stirred mixture of 3-hydroxy-8-methoxy-4,5-dihydronaphth[1,2-c]isoxazole (10.0g, 46.08mmol) in phosphorus oxychloride (12.8ml, 137.3mmol), triethylamine (6.42ml, 46.08mmol) was added dropwise. After completion of addition, the mixture was heated to reflux while stirring. After 4 hours, no starting material remained as shown by TLC [silica, EtOAc]. The mixture was cooled to room temperature, poured into 400ml of ice water, and extracted with heptane. The organic extracts were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Concentration of the filtrate *in vacuo* caused a solid to precipitate. The solid was triturated with heptane and dried *in vacuo* to provide the product as needles, mp of 55-57°C, homogeneous by TLC [silica, CH_2Cl_2, Rf=0.45]. The IR ($CHCl_3$), NMR ($CDCl_3$) and Mass Spectrum (M^+=235, EI, 70eV) were consistent with the structure. The yield was 7.75g (32.98mmol, 71.57%).

Elemental Analysis

	Calculated	Found
C	61.16	61.29
H	4.28	4.16
Cl	15.04	
N	5.94	5.90
O	13.58	

EXAMPLE 9

3-[(1-Methyl-4-piperidinyl)oxy]-4,5-dihydronaphth[1,2-c]isoxazole



To a stirred solution mixture of 4-hydroxy-N-methyl piperidine (5.05g, 43.89mmol) in 100ml of N-methylpyrrolidinone under N_2 was added NaH (1.75g of a 60% dispersion in oil, 43.89mmol). The mixture was stirred at room temperature for 15 minutes, then a solution of 3-chloro-4,5-dihydronaphth[1,2-c]isoxazole (3.0g, 14.63mmol) in 15ml N-methylpyrrolidinone was added in one portion. The stirred mixture was lowered into an oil bath preheated to 150°C. After 20 minutes TLC [CH_2Cl_2] showed no starting materials remaining. The mixture was removed from the heating bath and allowed to cool to room temperature. It was then partitioned between heptane/H_2O. The heptane phase was washed with water, dried over $MgSO_4$, filtered and concentrated *in vacuo*. This crude oil obtained was taken up in Et_2O, filtered, and the HCl salt precipitated by the addition of ethanolic HCl. This salt was recrystallized from CH_2Cl_2/Et_2O to

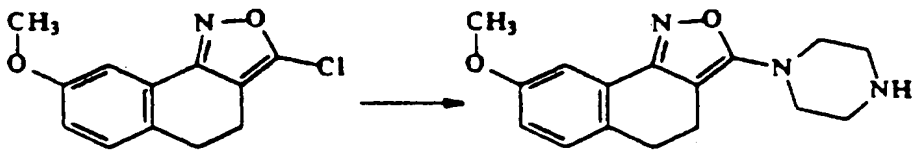
provide the product as a solid, mp of 147-150°C, homogeneous by TLC [silica, 1:1 CH_3OH:EtOAc, Rf=0.02]. The IR (KBr), NMR ($CDCl_3$) and Mass Spectrum (M^++1=285, CI, methane) were consistent with the structure. The yield was 1.2994g (4.05mmol, 36.09%).

Elemental Analysis

	Calculated	Found
C	63.65	63.55
H	6.60	6.63
Cl	11.05	
N	8.73	8.78
O	9.97	

EXAMPLE 10

3-(1-Piperazinyl)-8-methoxy-4,5-dihydronaphth[1,2-c]isoxazole



A stirred mixture of 3-chloro-8-methoxy-4,5-dihydronaphth[1,2-c]isoxazole (2.0g, 8.51mmol), piperazine (7.0g, 80.6mmol) and K_2CO_3 (2.4g, 17.1mmol) in 8.0ml of N-methylpyrrolidinone under N_2 was lowered into an oil bath preheated to 150°C. The mixture was heated while stirring under N_2 for 20 minutes. At that time TLC [CH_2Cl_2] showed no starting

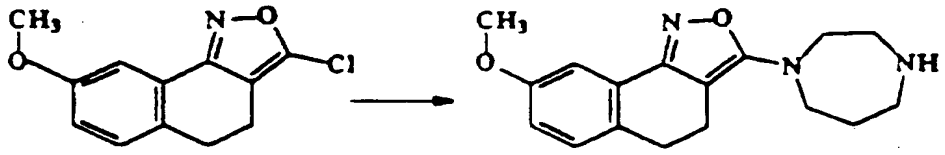
material remained. The mixture was removed from the heating bath and allowed to cool to room temperature. Upon dilution of the reaction mixture with H_2O, a solid precipitated which was collected and dried *in vacuo* to provide pure product, mp of 86-88°C, homogeneous by TLC [silica, 1:1 $CH_3OH:CH_2Cl_2$, Rf=0.37]. The IR ($CHCl_3$), NMR ($CDCl_3$) and Mass Spectrum (M^+=285, EI, 70eV) were consistent with the structure. The yield was 1.932g (6.78mmol, 79.66%).

Elemental Analysis

	Calculated	Found
C	67.35	66.99
H	6.71	6.77
N	14.73	14.53
O	11.21	

EXAMPLE 11

3-(1-Homopiperazinyl)-8-methoxy-4,5-dihydronaphth[1,2-c]isoxazole



A stirred mixture of 3-chloro-8-methoxy-4,5-dihydronaphth[1,2-c]isoxazole (2.66g, 11.32mmol), homopiperazine

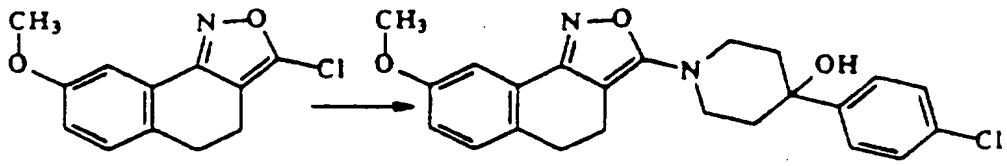
(11.40g, 113.2mol) and K_2CO_3 (3.13g, 22.68mmol) in 10.0ml of N-methylpyrrolidinone under N_2 was lowered into an oil bath preheated to 150°C. The mixture was heated while stirring under N_2 for 20 minutes. At that time, TLC (CH_2Cl_2) showed no starting material remained. The mixture was removed from the heating bath, allowed to cool to room temperature and diluted with H_2O, which caused a solid to precipitate. The crude solid was dried, recrystallized from Et_2O and dried *in vacuo* (0.1mm) at 85°C, to provide pure product, mp of 106-109°C, homogeneous by TLC [silica, 1:1 $CH_3OH:CH_2Cl_2$, Rf=0.18]. The IR ($CHCl_3$), NMR ($CDCl_3$) and Mass Spectrum (M^+=299, EI, 70eV) were consistent with the structure. The yield was 1.7948g (6.00mmol, 53.03%).

Elemental Analysis

	Calculated	Found
C	68.21	68.24
H	7.07	7.11
N	14.04	14.00
O	10.69	

EXAMPLE 12

3-(1-(4-(p-Chlorophenyl)-4-hydroxy-piperidinyl)-8-methoxy-4,5-dihydronaphth[1,2-c]isoxazole



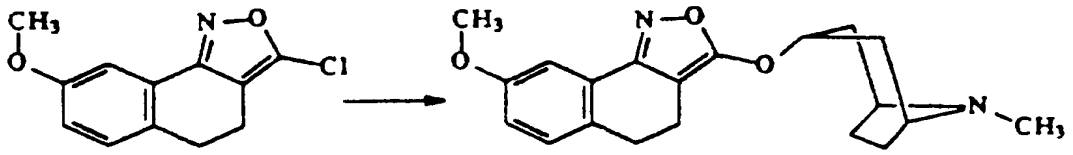
A stirred mixture of 3-chloro-8-methoxy-4,5-dihydronaphth(1,2-c)isoxazole (2.0g, 8.51mmol), 4-(p-chlorophenyl)-4-hydroxy-dipiperidine (3.6g, 17.02mol) and K_2CO_3 (2.35g, 17.02mmol) in 6ml of N-methylpyrrolidinone under N_2 was lowered into an oil bath preheated to 150°C. The mixture was heated while stirring under N_2 for 1 hour. At that time, TLC [CH_2Cl_2] showed no remaining starting material. The mixture was removed from the heating bath and allowed to cool to room temperature. Upon dilution of the reaction mixture with H_2O, a solid precipitated which was recrystallized from EtOAc and dried *in vacuo* (0.1mm) at 85°C to provide pure product, mp of 174-177°C, homogeneous by TLC [silica, 2:1 heptane:EtOAc, Rf=0.263]. The IR ($CHCl_3$), NMR ($CDCl_3$) and Mass Spectrum (M^+=410, E.I., 70eV) were consistent with the structure. The yield was 2.3798g (5.60mmol, 68.20%).

Elemental Analysis

	Calculated	Found
C	67.23	67.24
H	5.64	5.75
Cl	8.63	
N	6.82	8.78
O	11.68	

EXAMPLE 13

3-[(*endo*)-8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)oxy]-8-methoxy-4,5-dihydronaphth[1,2-c]isoxazole



To a stirred mixture of tropine (5.41g, 38.31mmol) in 10 ml of (THF) under N_2 at 0°C was slowly added n-BuLi (15.0ml of a 2.5M solution in hexanes, 38.31mmol). The mixture was stirred for 15 minutes while allowed to warm to room temperature, then a solution of 3-chloro-8-methoxy-4,5-dihydronaphth[1,2-c]isoxazole (3.0g, 12.76mmol) in 30ml N-methylpyrrolidinone was added in one portion. The internal temperature increased to 99-100°C and was maintained there. After 3 hours, TLC [CH_2Cl_2] showed no starting material remaining. The mixture was removed from the heating bath and allowed to cool to room temperature. It was then

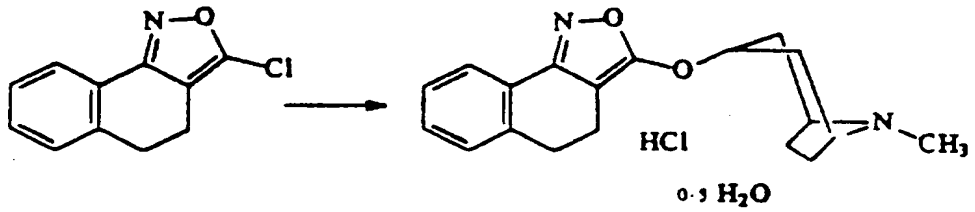
partitioned between heptane/H_2O. The heptane phase was washed with H_2O, dried over $MgSO_4$, filtered and concentrated *in vacuo*, whereupon it solidified. This crude solid was recrystallized from a minimum of heptane and dried *in vacuo* to provide the product as a solid, mp of 102-104°C, homogeneous by TLC [silica, 1:1 $CH_3OH:CH_2Cl_2$, Rf=0.20]. The IR ($CHCl_3$), NMR ($CDCl_3$) and Mass Spectrum ($M^{\cdot+}$=341, CI, methane) were consistent with the structure. The yield was 1.3729g (4.038mmol, 31.64%).

Elemental Analysis

	Calculated	Found
C	70.57	70.47
H	7.11	7.25
N	8.23	8.14
O	14.10	

EXAMPLE 14

3-[(*endo*-8-Methyl-8-azabicyclo[3.2.1]oct-3-yl)oxy]-4,5-dihydronaphth[1,2-c]isoxazole hydrochloride hemihydrate



To a stirred mixture of tropine (4.4g, 31.16mmol) in 10ml

of

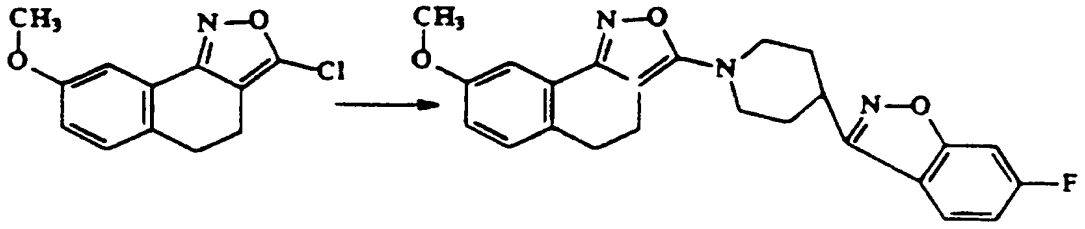
THF under N_2 at 0°C was slowly added n-BuLi (12.47ml of a 2.5M solution in hexanes, 31.16mmol). The mixture was stirred for 15 minutes while allowed to warm to room temperature, then a solution of 3-chloro-4,5-dihydronaphth[1,2-c]isoxazole (2.13g, 10.39mmol) in 30ml N-methylpyrrolidinone was added in one portion. The stirred mixture was lowered into an oil bath preheated to 150°C. The internal temperature increased to 85°C and was maintained there. After 3 hours, TLC [CH_2Cl_2] showed no remaining starting material. The mixture was removed from the heating bath and allowed to cool to room temperature. It was then partitioned between heptane/H_2O. The heptane phase was washed with H_2O, dried over $MgSO_4$, filtered and concentrated *in vacuo*, to provide the free base as an oil, which resisted attempts at crystallization. The oil was taken up in Et_2O and the HCl salt was precipitated by the addition of ethanolic HCl. This crude solid was recrystallized from Et_2O/CH_2Cl_2 and dried *in vacuo* at 85°C to provide the product as a solid, mp of 167-170°C, (darkens at ca. 150°C) homogeneous by TLC [silica, 1:1 $CH_3OH:CH_2Cl_2$, Rf=0.14]. The IR ($CHCl_3$), NMR ($CDCl_3$) and Mass Spectrum (M^++1=311, CI, methane) were consistent with the structure. Analysis and NMR confirmed the hemihydrate structure. The yield was 1.268g (3.563mmol, 34.29%).

Elemental Analysis

	Calculated	Found
C	64.12	64.25
H	6.80	6.77
Cl		
N	7.87	7.70
O	9.23	

EXAMPLE 15

3-(1-(4-(6-Fluorobenzisoxazol-3-yl)-piperidinyl)-8-methoxy-4,5-dihydronaphth[1,2-c]isoxazole



A stirred mixture of 3-chloro-8-methoxy-4,5-dihydronaphth[1,2-c]isoxazole (2.0g, 8.51mmol), 4-(6-fluorobenzisoxazol-3-yl)-piperidine (2.8g, 12.76mmol) and K_2CO_3 (2.35g, 17.02mmol) in 10ml of N-methylpyrrolidinone under N_2 was lowered into an oil bath preheated to 150°C. The mixture was heated while stirring under N_2 for 90 minutes. At that time TLC (CH_2Cl_2) showed no remaining starting material. The mixture was removed from the heating bath and allowed to cool to room

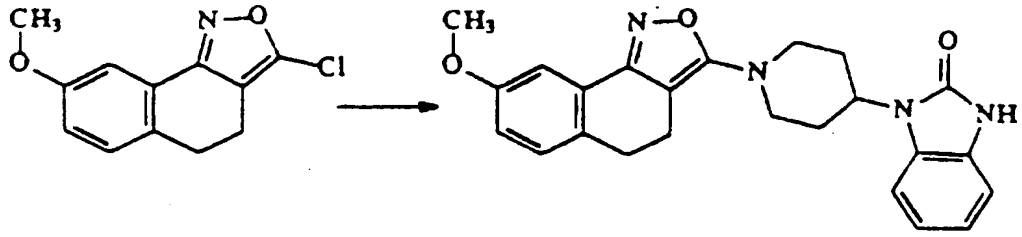
temperature. Upon dilution of the reaction mixture with H_2O, a solid precipitated which was collected, dried, dissolved in CH_2Cl_2 and filtered through neutral alumina. The fractions containing desired product were combined and concentrated, and the resultant solid obtained was triturated with Et_2O to provide a solid, mp of 181-183°C, homogeneous by TLC [silica, 2:1 Heptane:EtOAc, Rf=0.15]. The IR ($CHCl_3$), NMR ($CDCl_3$) and Mass Spectrum (M^+=419, EI, 70eV) were consistent with the structure. The yield was 1.1318g (2.70mmol, 31.70%).

Elemental Analysis

	Calculated	Found
C	68.72	68.47
H	5.29	5.28
F	4.53	
N	10.02	9.97
O	11.44	

EXAMPLE 16

3-(1-(4-2-Oxo-1-benzimidazolinyl)piperidinyl))-8-methoxy-4,5-dihydronaphth[1,2-c]isoxazole



A stirred mixture of 3-chloro-8-methoxy-4,5-dihydronaphth[1,2-c]isoxazole (2.57g, 10.9mmol), 4-(2-oxo-1-benzimidazolinyl)piperidine (4.74g, 21.8mmol) and K_2CO_3 (3.02g, 21.8mmol) in 12ml of N-methylpyrrolidinone under N_2 was lowered into an oil bath preheated to 150°C. The mixture was heated while stirring under N_2 for 4 hours. At that time, TLC (CH_2Cl_2) showed no remaining starting material. The mixture was removed from the heating bath and allowed to cool to room temperature. Upon dilution of the reaction mixture with H_2O, a solid precipitated which was collected, dried, dissolved in CH_2Cl_2 and filtered through neutral alumina using CH_2Cl_2 and then 1:1 CH_2Cl_2:Et_2O. The fractions containing desired product were combined and concentrated, and the resultant solid obtained was triturated with EtOAc and dried *in vacuo* (0.1mm Hg, 85°C) to provide a solid, mp of 211-214°C, homogeneous by TLC [silica,

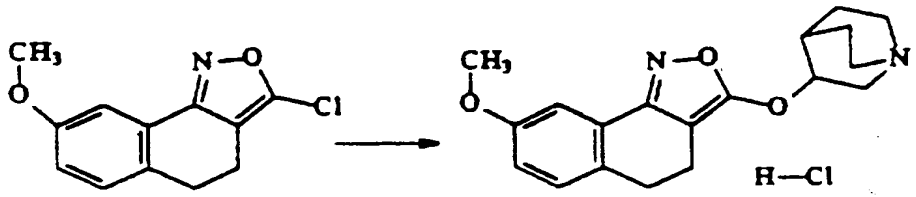
EtOAc, Rf=0.38]. The IR ($CHCl_3$), NMR ($CDCl_3$) and Mass Spectrum (M^+=416, EI, 70eV) were consistent with the structure. The yield was 1.602g (3.85mmol, 33.33%).

Elemental Analysis

	Calculated	Found
C	69.21	68.88
H	5.81	5.90
N	13.45	13.10
O	11.52	

EXAMPLE 17

3-[(Quinuclidin-3-yl)oxy]-8-methoxy-4,5-dihydronaphth[1,2-c]isoxazole hydrochloride



To a stirred mixture of 3-quinuclidinol (4.87g, 38.28mmol) in 10ml of THF under N_2 at 0°C was slowly added n-BuLi (15.32g of a 2.5M solution in hexanes, 38.28mmol). The mixture was stirred for 10 minutes while allowing to warm to room temperature, then a solution of 3-chloro-8-methoxy-4,5-dihydronaphth[1,2-

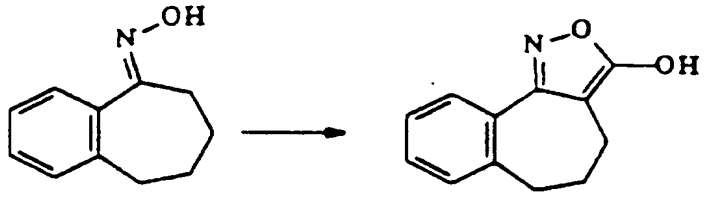
c]isoxazole (3.0g, 12.76mmol) in 30ml N-methylpyrrolidinone was added in one portion. The stirred mixture was lowered into an oil bath preheated to 150°C. The internal temperature increased to 85°C and was maintained there. After 3 hours, TLC [CH_2Cl_2] showed no remaining starting material. The mixture was removed from the heating bath and allowed to cool to room temperature. It was then partitioned between heptane/H_2O. The heptane phase was dried over $MgSO_4$, filtered and concentrated *in vacuo* to provide the free base as an oil. The oil was taken up in Et_2O and the HCl salt was precipitated by the addition of ethanolic HCl. This solid was collected and dried *in vacuo* (0.1mm Hg, 85°C) to provide the product as a solid, mp of 133-136°C, homogeneous by TLC [silica, 1:1 $CH_3OH:CH_2Cl_2$, Rf=0.23]. The IR (KBr), NMR (DMSO-d_6) and Mass Spectrum (M^++1=326, EI, 70eV) were consistent with the structure. The yield was 0.965g (2.39mmol, 18.79%).

Elemental Analysis

	Calculated	Found
C	62.89	62.91
H	6.39	6.28
Cl	9.77	
N	7.72	7.51
O	13.23	

EXAMPLE 18

5,6-Dihydro-4H-benzo[6,7]cyclohept[1,2-c]isoxazol-3-ol



To a mechanically-stirred mixture of 1-benzosuberone oxime (10.0g, 57.1mmol) in anhydrous THF (200ml) at 0°C under N_2 was slowly added n-BuLi (50.3ml of a 2.5M solution in hexane, 125.62mmol). The mixture was stirred at 0°C for 30 minutes, then CO_2 gas was bubbled into the solution. After 15 minutes, CO_2 addition was stopped and N_2 flow was restored. The thick mixture was stirred and warmed slowly to room temperature for 1½ hours, then 6N H_2SO_4 (220ml) was slowly added, which dissolved the solids. Stirring was continued for 18 hours, at which time the TLC [EtOAc] showed a mixture of starting oxime and product (starting oxime was best visualized using 2:1 heptane:EtOAc eluent). The mixture was poured into a separatory funnel, and the organic phase drawn off. The aqueous phase was extracted with EtOAc, and the organic phase and the EtOAc extracts were combined, washed with H_2O, dried over $MgSO_4$ and filtered. Concentration *in vacuo* caused the precipitation of a solid which was collected and dried *in vacuo* to provide the product as a

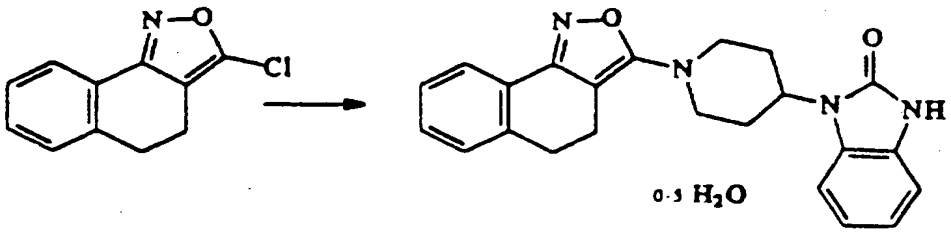
solid, mp of 165-168°C, homogeneous by TLC [silica, Et_2O, Rf=0.28]. The IR (KBr), NMR (DMSO-d_6) and Mass Spectrum (M^+=201, EI, 70 eV) were consistent with the structure. The yield was 3.0324g (15.09mmol, 26.42%).

Elemental Analysis

	Calculated	Found
C	71.63	71.45
H	5.51	5.50
N	6.96	6.91
O	15.90	

EXAMPLE 19

3-(1-(4-(2-Oxo-1-benzimidazolinyl)piperidinyl))-4,5-dihydronaphth[1,2-c]isoxazole hemihydrate



A stirred mixture of 3-chloro-4,5-dihydronaphth[1,2-c]isoxazole (3.1g, 15.12mmol), 4-(2-oxo-1-benzimidazolinyl)-piperidine (8.2g, 37.8mmol) and K_2CO_3 (4.2g, 30.24mmol) in 18ml of N-methylpyrrolidinone under N_2 was lowered into an oil bath

preheated to 150°C. The mixture was heated while stirring under N_2 for 90 minutes. At that time, TLC (CH_2Cl_2) showed no remaining starting material. The mixture was removed from the heating bath and allowed to cool to room temperature. Upon dilution of the reaction mixture with H_2O, a solid precipitated which was collected, dried, dissolved in CH_2Cl_2 and filtered through neutral alumina using CH_2Cl_2 and then 1:1 CH_2Cl_2:Et_2O. The fractions containing desired product were combined and concentrated, and the solid obtained was recrystallized from EtOAc and dried *in vacuo* (0.1mm Hg, 110°C) to provide a solid, mp of 229-233°C, homogeneous by TLC [silica, EtOAc, Rf=0.54]. The IR (KBr), NMR ($CDCl_3$) and Mass Spectrum (M^+=386, EI, 70eV) were consistent with the structure. Analysis and NMR confirmed a hemihydrate structure. The yield was 1.103g (2.79mmol, 18.45%).

Elemental Analysis

	Calculated	Found
C	69.82	70.25
H	5.86	5.64
N	14.17	14.22
O	8.28	

Preferred pharmaceutically acceptable addition salts include salts of inorganic acids such as hydrochloric, hydrobromic, sulfuric, nitric, phosphoric and perchloric acids; as well as organic acids such as tartaric, citric, acetic, succinic, maleic, fumaric, and oxalic acids.

The active compounds of the present invention may be administered orally, for example, with an inert diluent or with an edible carrier. They may be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the compounds may be incorporated with excipients and used in the form of tablets, troches, capsules, elixirs, suspensions, syrups, waters, chewing gums and the like. These preparations should contain or form at least 0.5% of active compound, but may be varied depending upon the particular form and may conveniently be from about 4 to about 75% of the weight of the unit. The amount of compound present in such composition is such that a suitable dosage of active compound will be obtained. Preferred compositions and preparations according to the present invention are prepared so that an oral dosage unit form contains from about 1.0 to about 300mgs of active compound.

The tablets, pills, capsules, troches and the like may also contain the following ingredients: a binder such as

microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel™, corn starch and the like; a lubricant such as magnesium stearate or Sterotex®; a glidant such as colloidal silicon dioxide; and a sweetening agent such as sucrose or saccharin or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring may be added. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as fatty oil. Other dosage unit forms may contain other various materials which modify the physical form of the dosage unit, for example, as coatings. Thus tablets or pills may be coated with sugar, shellac, or other enteric coating agents. A syrup may contain, in addition to the active compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings an flavors. Materials used in preparing these various compositions should be pharmaceutically pure and non-toxic in the amounts used.

For the purpose of parenteral therapeutic administration, the active compounds of the invention may be incorporated into a solution or suspension. These preparations should contain at least 0.1% of the aforesaid compound, but may be varied from about 0.5 to about 30% of the weight thereof. The amount of compound in such composition is such that a suitable dosage of active compound will be obtained. Preferred compositions and

preparations according to the invention are prepared so that a parenteral dosage unit contains from about 0.5 to about 100mgs of active compound.

The solutions or suspensions may also include the following components; a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as EDTA; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. The parenteral preparation can be enclosed in ampules, disposable syringes or multiple dose vials made of glass or plastic.

The compounds of the invention may be useful as 5-HT, antagonists on the coronary chemoreflex for the treatment of anxiety, psychiatric disorders, nausea and vomiting by virtue of their ability to bind to rat entorhinal cortex membranes.

^{3}H-GR 65630 Binding to Rat Entorhinal Cortex Membranes

Studies have been performed to determine the affinity of the compounds of the invention for the 5HT, binding site in the brain. This study or assay may be useful for predicting the

potential of compounds to exhibit antiemetic, anxiolytic or atypical antipsychotic profiles.

Originally, it was believed that 5HT$_3$ binding sites existed only in the periphery. However, with the recent introduction of potent and selective 5HT$_3$ antagonist drugs such as GR65630, Zacopride, ICS 205 930 and MDL 72222 (Bemesetron, $C_{15}H_{17}Cl_2NO_2$), data from binding studies have indicated that 5HT$_3$ binding sites are also located in selected areas of the brain. The highest levels of 5HT$_3$ binding sites have been detected in limbic and dopamine containing brain areas (entorhinal cortex, amygdala, nucleus accumbens and tuberculum olfactorium) (Kilpatrick, G.J. *et al.* Identification and distribution of 5HT$_3$ receptors in rat brain using radioligand binding. **Nature** 330: 746-748). Besides possessing selective binding in dopamine rich areas, 5HT$_3$ antagonists have been reported to block behavioral effects associated with certain drugs of abuse (nicotine and morphine) and to be active in behavioral tests predictive of anxiolytic activity. Based on these selective regional binding results and behavioral studies, 5HT$_3$ antagonists may have a therapeutic benefit in disease states believed to be associated with excessive dopaminergic activity, i.e., schizophrenia, anxiety and drug abuse.

In accordance with the above-discussed assay, a 0.05M of Krebs-Hepes buffer, pH 7.4 was prepared as follows:

11.92g	Hepes
10.52g	NaCl
0.373g	KCl
0.277g	$CaCl_2$
0.244g	$MgCl_2.6H_2O$

q.s. to 1 liter with distilled H_2O, bring pH up to 7.4 (at 4°C) with 5N NaOH

[^{3}H]-GR65630 (87.0Ci/mmol) was obtained from New England Nuclear. For IC_{50} determinations: [^{3}H]-GR65630 was made up to a concentration of 1.0nM in Krebs-Hepes buffer such that when 100μl is added to each tube, a final concentration of 0.4nM is attained in the 250μl assay.

GR38032F was obtained from Research Biochemical Inc. GR38032F was made up to a concentration of 500μM in Krebs-Hepes buffer. 50μl of Krebs-Hepes were added to each of 3 tubes for determination of nonspecific binding (yields a final concentration of 100μM in the 250μl assay).

For most assays, a 50μl stock solution was prepared in a suitable solvent and serially diluted with Krebs-Hepes buffer

such that when 50μl of drug is combined with the total 250μl assay, a final concentration from 10^{-5} to 10^{-9}M was attained. Characteristically, seven concentrations may be used for each assay; however, higher or lower concentrations may be used, depending on the potency of the drug.

During tissue preparation, Male Wistar rats (15-200g) were decapitated, the entorhinal cortex removed, weighed and homogenized in 10 volumes of ice cold 0.05M Krebs-Hepes buffer, pH 7.4. The homogenate is centrifuged at 48,000g for 15 minutes at 4°C. The resulting pellet was rehomogenized in fresh Krebs-Hepes buffer and recentrifuged at 48,000g for 15 minutes at 4°C. The final pellet was resuspended in the original volume of ice-cold Krebs-Hepes buffer. This yielded a final tissue concentration of 1.2 to 1.6mg/ml with the addition of 100μl to the assay. Specific binding was approximately 55 to 65% of the total bound ligand.

In conducting the assay, the following volumes were utilized:

100μl	of Tissue suspension;
100μl	of [^{3}H]-GR65630; and
50μl	500M GR38032F (Vehicle for binding) or appropriate drug concentration

Sample tubes were kept on ice for additions, then vortexed and incubated with continuous shaking for 30 minutes at 37°C. At the end of the incubation period, the incubate is diluted with 5 ml of ice-cold Krebs-Hepes buffer and immediately vacuum filtered through Whatman GF/B filters, followed by two 5ml washes with ice-cold Krebes-Hepes buffer. The filters are dried and counted in 10 ml of liquid scintillation cocktail. Specific GR 65630 binding is defined as the difference between the total binding and that bound in the presence of 100μM GR38032F. IC_{50} values were derived from computer-derived log-probit analysis.

Various compounds of the invention were subjected to the above-described assay and the results the affinity for 5 HT, receptors are reported in Table I, below.

TABLE I

Affinity for 5-HT, Receptor-Displacement of ^{3}H-GR 65630

Compound	IC_{50}, μM
Ex. 3	0.868
Ex. 4	0.083
Ex. 5	0.056

Ondansetron (standard)	0.089
ICS 205 930 (standard)	0.039

Measurement of 5 HT, Antagonist Effects in the Bezold-Jarisch Assay

This assay evaluates the effect of these compounds as 5-HT, antagonists. They were examined in this assay on the coronary chemoreflex (Bezold-Jarisch) initiated by 5-HT, *in vivo* and characterized by leading inhibition of sympathetic outflow and increased activity of the cardiac vagus, leading to profound bradycardia and hypotension. The values obtained allow for continuous monitoring of arterial pressure and heart rate responses by these compounds over an extended period of time to determine their effecicy for 5 HT, antagonism.

The catheters were prepared from Tygon tubing (45cm length, 0.05mm, ID) bonded to Teflon tubing (0.38mm, ID). The mechanical bonding was achieved by insertion of the Teflon tubing (5mm) into the dilated (ethylene dichloride, 3-4 min.) tip of the Tygon tubing. The junction was then sealed with vinyl glue, the catheters were soaked in cold sterilization solution (Amerse instrument germicide) and flushed thoroughly

with saline prior to implantation.

Long Evans rats were anesthetized with sodium pentobarbital (50mg/kg, ip). The catheters filled with hepranized saline (100 U/ml) were inserted in the left femoral artery and vein and passed into the abdominal aorta and inferior vena cava, respectively. The catheters were then sutured to the underlying muscle and the free ends were passed subcutaneously and exteriorized through an incision on the top of the skull. The catheters were then secured to the skin with sutures, nitrofurazone powder was dusted over the area of the incision and the incision was closed using 3-O silk sutures. The catheters were flushed with saline and sealed with metal obturators. Patentcy of the two catheters was maintained by daily flushing with hepranized saline (0.2 ml of 100 U/ml). The rats were given 48 hours recovery prior to obtaining cardiovascular data.

In the anesthetized rat model the catheters were not exteriorized, data was collected acutely under the influence of general anesthesia.

The baseline data Arterial Blood Pressure(mm Hg, systolic/diastolic) and Heart Rate (beats/min) were recorded and the rats were injected with 5-HT (3-7.5ug/kg, iv). The

individual response to the 5-HT intervention was determined and the compound was then administered singlely or in an ascending dose range. The rats were challenged with 5-HT again at intervals postdosing and the peak response was recorded.

Several compounds of the invention were tested according to the above-described assay and the results are reported in Table II, below.

TABLE II

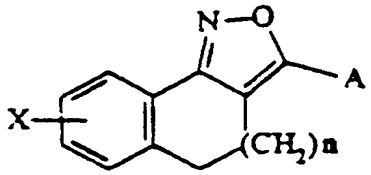
Inhibitory Potency of 5-HT_3 Antagonists on Reflex Bradycardia Induced by Intravenous 5-HT_3 in the Anesthetized Long-Evans Rat

Compound	Dose, mg/kg, ip	% Inhibition of Bezold-Jarisch Reflex (Values are mean ± SEM, 2-3 rats/dose)
Ondansetron	3.0	57.3 ± 9.7
Ondansetron	10.0	94.6 ± 2.7
Ex. 4	0.03	58.6 ± 16.4
Ex. 4	0.05	83.3 ± 8.2
Ex. 4	0.10	93.0 ± 1.0
Ex. 5	1.0	55.6 ± 9.7
Ex. 5	3.0	89.3 ± 2.9

In accordance with Table II, maximal reductions in heart rate induced by 5HT_3 (e.g. Bezold-Jarisch reflex) occurred 15 to 60 minutes after administration.

I Claim:

1. A compound of the formula:



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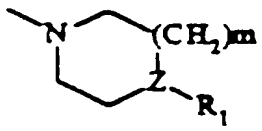
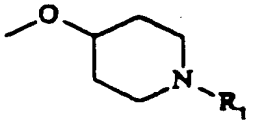
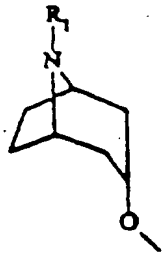
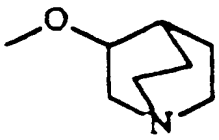
where A is hydrogen, hydroxy,







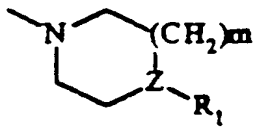
or



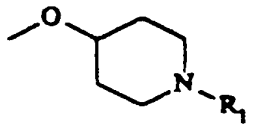
where R_1 is hydrogen, an alkyl group of 1 to 6 carbons, optionally substituted with hydroxy, alkoxy or amino substitution; aryl or heteroaryl, optionally substituted

with halogen, hydroxy or alkoxy; or benzyl optionally substituted with halogen, hydroxy or alkoxy; n is an integer of 1 or 2; Z is N, CH or C(OH); m is an integer of 1 to 3; and X is hydrogen, hydroxy or alkoxy; and the pharmaceutically acceptable salts thereof, and its geometric or optical isomers, or the racemic mixtures, where applicable.

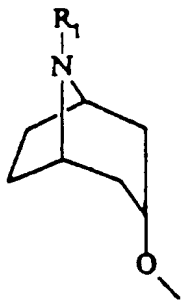
2. The compound according to Claim 1, wherein A is



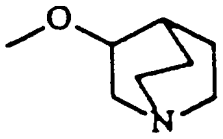
3. The compound according to Claim 1, wherein A is



4. The compound according to Claim 1, wherein A is



5. The compound according to Claim 1, wherein A is



6. The compound according to Claim 1, which is 3-chloro-4,5-dihydronaphth[1,2-c] isoxazole, its salts, isomers and racemic mixtures, where applicable.

7. The compound according to Claim 1, which is 3-hydroxy-8-methoxy-4,5-dihydronaphth[1,2-c]isoxazole, its salts, isomers and racemic mixtures, where applicable.

8. The compound according to Claim 1, which is 3-chloro-8-methoxy-4,5-dihydronaphth[1,2-c]isoxazole, its salts, isomers and racemic mixtures, where applicable.

9. The compound according to Claim 1, which is 5,6-dihydro-4H-benzo[6,7]cyclohept[1,2-c]isoxazol-3-ol, its salts, isomers and racemic mixtures, where applicable.

10. The compound according to Claim 2, which is 3-(4-methyl-1-piperazinyl)-4,5-dihydronaphth[1,2-c]isoxazole, its salts, isomers and racemic mixtures, where applicable.

11. The compound according to Claim 2, which is 3-(4-(2-hydroxy ethyl)-1-piperazinyl)-4,5-dihydronaphth[1,2-c]isoxazole, its salts, isomers and racemic mixtures, where applicable.

12. The compound according to Claim 2, which is 3-(1-homopiperazinyl)-4,5-dihydronaphth[1,2-c]isoxazole, its salts, isomers and racemic mixtures, where applicable.

13. The compound according to Claim 2, which is 3-(1-piperazinyl)-4,5-dihydronaphth[1,2-c]isoxazole, its salts, isomers and racemic mixtures, where applicable.

14. The compound according to Claim 2, which is 3-(4-benzyl-1-piperazinyl)4,5-dihydronaphth[1,2-c]isoxazole, its salts, isomers and racemic mixtures, where applicable.

15. The compound according to Claim 2, which is 3-(1-

piperazinyl)-8-methoxy-4,5-dihydronaphth[1,2-c]isoxazole, its salts, isomers and racemic mixtures, where applicable.

16. The compound according to Claim 2, which is 3-(1-homopiperazinyl)-8-methoxy-4,5-dihydronaphth[1,2-c]isoxazole, its salts, isomers and racemic mixtures, where applicable.

17. The compound according to Claim 2, which is 3-(1-(4-(p-chlorophenyl)-4-hydroxy-piperidinyl)-8-methoxy-4,5-dihydronaphth[1,2-c]isoxazole, its salts, isomers and racemic mixtures, where applicable.

18. The compound according to Claim 2, which is 3-(1-(4-(6-fluorobenzisoxazol-3-yl)-piperidinyl)-8-methoxy-4,5-dihydronaphth[1,2-c]isoxazole, its salts, isomers and racemic mixtures, where applicable.

19. The compound according to Claim 2, which is 3-(1-(4-2-oxo-1-benzimidazolinyl)piperidinyl))-8-methoxy-4,5-dihydronaphth[1,2-c]isoxazole, its salts, isomers and racemic mixtures, where applicable.

20. The compound according to Claim 2, which is 3-(1-(4-(2-oxo-1-benzimidazolinyl)piperidinyl))-4,5-dihydronaphth[1,2-

c]isoxazole hemihydrate, its salts, isomers and racemic mixtures, where applicable.

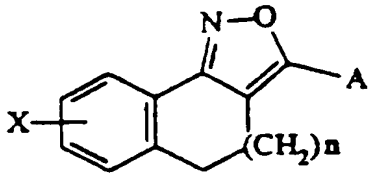
21. The compound according to Claim 3, which is 3-[(1-methyl-4-piperidinyl)oxy]-4,5-dihydronaphth[1,2-c]isoxazole, its salts, isomers and racemic mixtures, where applicable.

22. The compound according to Claim 4, which is 3-[(*endo*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)oxy]-8-methoxy-4,5-dihydronaphth[1,2-c]isoxazole, its salts, isomers and racemic mixtures, where applicable.

23. The compound according to Claim 4, which is 3-[(*endo*-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)oxy]-4,5-dihydronaphth[1,2-c]isoxazole hydrochloride hemihydrate, its salts, isomers and racemic mixtures, where applicable.

24. The compound according to Claim 5, which is 3-[(quinuclidin-3-yl)oxy]-8-methoxy-4,5-dihydronaphth[1,2-c]isoxazole hydrochloride, its salts, isomers and racemic mixtures, where applicable.

25. A method of preparing a compound of the formula:



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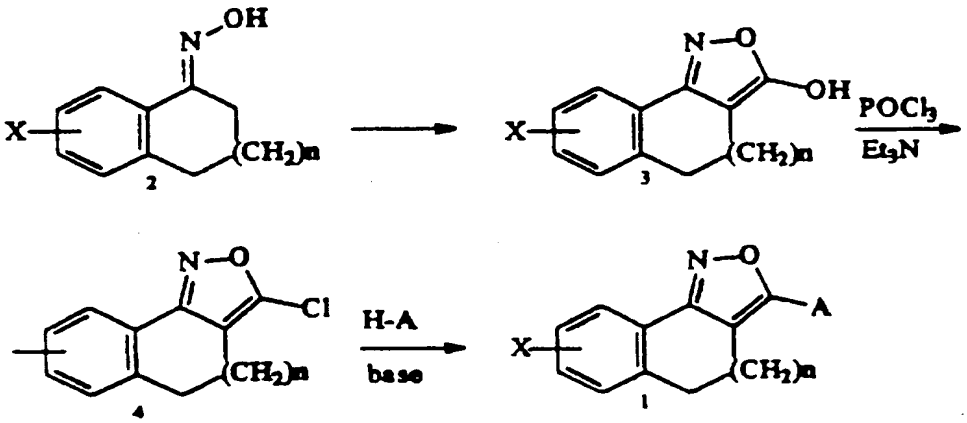
comprising the sequential reaction steps of:



26. A method of treating a patient in need of relief from a psychiatric disorder, nausea, vomiting and control of drug use, comprising providing to said patient an effective amount of the compound of Claim 1.

27. A method of treating a condition ameliorated by the use of a 5-HT_3 antagonist, comprising administering to a patient an effective amount to relief said condition of the compound of claim 1.

28. A pharmaceutical composition, comprising an effective amount of the compound of Claim 1, and a pharmaceutically acceptable carrier therefor.

29. A compound of Claim 1 for use as an active pharmaceutical substance.

30. The use of a compound of Claim 1 for the production of a medicament for the treatment of psychiatric disorders, nausea, vomiting and control of drug use.

31. The use of a compound of Claim 1 for the production of a medicament for the treatment of a condition ameliorated by the use of a 5-HT_3 antagonist.

INTERNATIONAL SEARCH REPORT

Intern. ial Application No
PCT/US 96/19569

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D261/20 C07D453/02 A61K31/42 C07D413/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"&" document member of the same patent family

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Date of the actual completion of the international search	Date of mailing of the international search report
28 April 1997	23.05.1997

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Herz, C

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Y	WO 94 10162 A (MERCK, SHARP & DOHME LTD.) 11 May 1994 see claims 1-11	1-31
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A	DE 21 19 977 A (TEIKOKU HORMONE MANUFACTURING CO., LTD.) 16 December 1971 see page 13, line 16 - line 20; claims 1-27	1-31
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